

Corporate Medical Policy

Extracorporeal Photopheresis after Solid-Organ Transplant and for Graft-versus-Host Disease, Autoimmune Disease, and Cutaneous T-Cell Lymphoma

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Description of Procedure or Service

Extracorporeal photopheresis (ECP) is a leukapheresis-based immunomodulatory procedure that involves the following steps:

1. Patient blood is collected into a centrifuge system that separates the leukocyte-rich portion (buffy coat) from the rest of the blood.
2. The photosensitizer agent 8-methoxypsoralen (8-MOP) is added to the lymphocyte fraction, which is then exposed to ultraviolet (UV) A (320-400 nm wavelength) light at a dose of 1-2 J per square cm.
3. The light-sensitized lymphocytes are reinfused into the patient.

ECP has been investigated for the treatment of patients with a variety of autoimmune diseases, graft-versus-host disease (GVHD), and cutaneous T-cell lymphoma (CTCL), as well as treatment for and prevention of organ rejection after solid-organ transplant.

Treatment for and Prevention of Organ Rejection after Solid-Organ Transplant

The standard of care for treatment of organ transplant rejection is immunosuppression, with the particular regimen dictated by the organ being transplanted. As organ transplantation success rates have improved, more patients are facing the morbidity and mortality associated with immunosuppressive therapies developed to prevent rejection of the transplanted organ. Immunosuppressive therapies are used to lower the responsiveness of the recipient's immune system, decreasing the chance of rejection. Unfortunately, portions of the immune system responsible for the prevention of viral, fungal, and bacterial infection are also affected. This can, in turn, lead to serious infections, including opportunistic infections.

While first approved for the treatment of CTCL, ECP has more recently been used as a supplement to conventional therapies in the area of transplantation.

Reports of the successful use of ECP in human cardiac transplant recipients were published in 1992 and use in other transplant patients followed. Although the specific mechanism of action of ECP is unknown, the reinfusion of treated leukocytes seems to specifically suppress the patient's immune response to the donor organ, while maintaining the body's ability to respond to other antigens. The specificity of ECP to target the immune response to the transplanted organ allows ECP to decrease organ rejection without an increased risk of infection, common with immunosuppressant drugs.

Treatment of Graft-versus-Host Disease (GVHD)

ECP as a treatment of GVHD after a prior allogeneic stem-cell transplant is based on the fact that

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GVHD is an immunologically mediated disease. GVHD can be categorized into acute disease, occurring within the first 100 days after infusion of allogeneic cells, or chronic disease, which develops sometime after 100 days. Acute GVHD is commonly graded from I–IV, ranging from mild disease, which is characterized by a skin rash without involvement of the liver or gut, to grades III and IV, which are characterized by generalized erythroderma, elevated bilirubin levels, or diarrhea. Grade III acute GVHD is considered severe, while Grade IV is considered life threatening. Chronic GVHD typically presents with more diverse symptomatology resembling autoimmune diseases such as progressive systemic sclerosis, systemic lupus erythematosus, or rheumatoid arthritis. Chronic GVHD may affect the mouth, eyes, respiratory tract, musculoskeletal system, peripheral nerves, as well as the skin, liver, or gut—the usual sites of acute GVHD.

Treatment of Autoimmune Disease

The use of ECP as a treatment of autoimmune disease is based on the premise that pathogenic lymphocytes form an expanded clone of cells, which are damaged when exposed to UV light in the presence of 8-MOP. It is hypothesized that the resulting damage induces a population of circulating suppressor T-cells targeted against the light-damaged cells. It is further hypothesized that these suppressor T-cells are targeted at a component of the cell that is common to the entire clone of abnormal cells (i.e., not just the light-sensitized cells), thus inducing a systemic effect. However, although scleroderma and other autoimmune diseases are associated with the presence of circulating antibodies, it is not certain how these antibodies are related to the pathogenesis of the disease, and, as discussed in this policy, photopheresis is not associated with consistent changes in autoantibody levels.

Treatment of Cutaneous T-Cell Lymphoma

According to the National Cancer Institute, cutaneous T-cell lymphoma (CTCL) is a neoplasia of malignant T-lymphocytes that initially present as skin involvement. CTCL is extremely rare, with an estimated incidence of about 0.4 per 100,000 annually but, because most are low-grade malignancies with long survival, the overall prevalence is much higher. Two CTCL variants, mycosis fungoides and the Sezary syndrome, account for about 60% and 5% of new cases of CTCL, respectively.

CTCL is included in the Revised European-American Lymphoma classification as a group of low-grade T-cell lymphomas, which should be distinguished from other T-cell lymphomas that involve the skin, such as anaplastic large cell lymphoma, peripheral T-cell lymphoma, adult T-cell leukemia/lymphoma (usually with systemic involvement), or subcutaneous panniculitic T-cell lymphoma. In addition, a number of benign or very indolent conditions can be confused with mycosis fungoides, further complicating diagnosis. See the Policy Guidelines for the current staging classification of CTCL using the TNM (tumor, node, metastasis) classification system.

Mycosis fungoides typically progresses from an eczematous patch/plaque stage covering less than 10% of the body surface (T1) to plaque stage covering 10% or more of the body surface (T2), and finally to tumors (T3) that frequently undergo necrotic ulceration. Sezary syndrome is an advanced form of mycosis fungoides with generalized erythroderma (T4) and peripheral blood involvement (B1) at presentation. Cytologic transformation from a low-grade lymphoma to a high-grade lymphoma sometimes occurs during the course of these diseases and is associated with a poor prognosis. A common cause of death during the tumor phase is sepsis from *Pseudomonas aeruginosa* or *Staphylococcus aureus* caused by chronic skin infection with staphylococcus species and subsequent systemic infections.

The natural history of mycosis fungoides is typically indolent. Symptoms may present for long periods, an average of 2 to 10 years, as waxing and waning cutaneous eruptions prior to biopsy confirmation. The prognosis of patients with mycosis fungoides/Sezary syndrome is based on the

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extent of disease at presentation and its stage. Lymphadenopathy and involvement of peripheral blood and viscera increase in likelihood with worsening cutaneous involvement and define poor prognostic groups. The median survival following diagnosis varies according to stage. Patients with stage IA disease have a median survival of 20 or more years, with the majority of deaths for this group typically unrelated to mycosis fungoides. In contrast, more than 50% of patients with stage III through stage IV disease die of their disease, with a median survival of less than 5 years.

Appropriate therapy of CTCL depends on a variety of factors, including stage, the patient's overall health, and the presence of symptoms. In general, therapies can be categorized into topical and systemic treatments that include ECP. In contrast to more conventional lymphomas, CTCL, possibly excepting ones in the earliest stages, is not curable. Thus, systemic cytotoxic chemotherapy is avoided except for advanced-stage cases. Partial or complete remission is achievable, although the majority of patients require lifelong treatment and monitoring.

Regulatory Status

In the U.S., the UVAR® XTS Photopheresis System was approved via premarket application (PMA) by the U.S. Food and Drug Administration (FDA) for use in the ultraviolet-A (UVA) irradiation (in the presence of the photoactive drug, methoxsalen) of extracorporeally circulating leukocyte-enriched blood in the palliative treatment of the skin manifestations of cutaneous T-cell lymphoma (CTCL) in persons who have not been responsive to other therapy.

8-MOP (UVADEX®) is approved by the FDA for use in conjunction with UVAR XTS Photopheresis System for use in the UVA irradiation in the presence of the photoactive drug methoxsalen of extracorporeally circulating leukocyte-enriched blood in the palliative treatment of the skin manifestations of CTCL in persons who have not been responsive to other therapy.

The use of the UVAR® XTS Photopheresis System or UVADEX® for other conditions is an off-label use of a FDA-approved device/drug.

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for extracorporeal photopheresis when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

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When Extracorporeal Photopheresis is covered

Organ Rejection after Solid-Organ Transplant

Extracorporeal photopheresis may be considered medically necessary to treat cardiac allograft rejection, including acute rejection, that is either recurrent or that is refractory to standard immunosuppressive drug treatment.

Graft-Versus-Host Disease

Extracorporeal photopheresis may be considered medically necessary as a technique to treat chronic graft-versus-host disease that is refractory to medical therapy.

Cutaneous T-cell lymphoma

Extracorporeal photopheresis may be considered medically necessary as a technique to treat late-stage (III/IV) cutaneous T-cell lymphoma.

Extracorporeal photopheresis may be considered medically necessary as a technique to treat early stage (I/II) cutaneous T-cell lymphoma that is progressive and refractory to established nonsystemic therapies.

When Extracorporeal Photopheresis is not covered

Organ Rejection after Solid-Organ Transplant

Extracorporeal photopheresis is considered investigational in all other situations related to treatment or prevention of rejection in solid-organ transplantation.

Graft-Versus-Host Disease

Extracorporeal photopheresis is considered investigational as a technique to treat acute graft-versus-host disease or chronic graft-versus-host disease that is either previously untreated or is responding to established therapies.

Autoimmune Diseases

Extracorporeal photopheresis is considered investigational as a technique to treat either the cutaneous or visceral manifestations of autoimmune diseases, including but not limited to scleroderma, systemic lupus erythematosus, rheumatoid arthritis, pemphigus, psoriasis, multiple sclerosis, diabetes or autoimmune bullous disorders.

Cutaneous T-cell lymphoma

Extracorporeal photopheresis is considered investigational as a technique to treat early stage (I/II) cutaneous T-cell lymphoma that is either previously untreated or is responding to established nonsystemic therapies.

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Policy Guidelines

A regimen of immunosuppressive therapy is standard of care for the treatment of solid-organ rejection. Therefore, refractory rejection is defined as rejection that fails to respond adequately to a standard regimen of immunosuppressive therapy.

Recurrent allograft rejection is defined as having at least 2 rejection episodes that recurred after standard immunosuppressive therapy.

An alternating regimen of cyclosporine and prednisone is commonly used to treat chronic graft-versus-host disease. Other therapies include antithymocyte globulin, corticosteroid monotherapy, and cytotoxic immunosuppressive drugs such as procarbazine, cyclophosphamide, or azathioprine. Therefore, refractory disease is defined as chronic graft-versus-host disease that fails to respond adequately to a trial of any of the above therapies.

There is no standard schedule for extracorporeal photopheresis. However, most reported schedules initiate therapy with 1–3 days of extracorporeal photopheresis at 1- to 3-week intervals, followed by a tapering of therapy. When extracorporeal photopheresis is used as single agent to treat CTCL, it is most often given on 2 consecutive days every 3-4 weeks.

Cutaneous T-cell Lymphoma (CTCL) Staging (based on the TNM classification system)

IA: T1N0M0

IB: T2N0M0

IIA: T1-2N1M1

IIB: T3N0,1M0

III: T4N0-1M0

IVA: T1-4N2-3M0

IVB: T1-4N0-3M1

According to the World Health Organization-European Organization for Research and Treatment of Cancer (WHO-EORTC), Sezary syndrome is defined by the triad of erythroderma, generalized lymphadenopathy, and the presence of neoplastic T-cells (Sezary cells) in skin, lymph nodes, and peripheral blood. The International Society of Cutaneous Lymphomas recommends an absolute Sezary cell count of at least 1,000 cells per cubic mm, in the presence of immune-phenotypical abnormalities (CD4/CD8 ratio greater than 10, loss of any or all of the T-cell antigens CD2, CD3, CD4, and CD5, or both), or the demonstration of a T-cell clone in the peripheral blood by molecular or cytogenetic methods.

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Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 36522

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.36, 12/11/2009

Medical Director Review - 8/2010

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.36, 1/13/2011

Medical Director Review – 3/2011

Specialty Matched Consultant Advisory Panel – 8/2011

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.36, 3/8/2012

Policy Implementation/Update Information

9/28/10 New policy written. “Extracorporeal photopheresis may be considered medically necessary as a technique to treat chronic graft-versus-host disease that is refractory to medical therapy. Extracorporeal photopheresis may be considered medically necessary as a technique to treat late-stage (III/IV) cutaneous T-cell lymphoma. Extracorporeal photopheresis may be considered medically necessary as a technique to treat early stage (I/II) cutaneous T-cell lymphoma that is progressive and refractory to established nonsystemic therapies.” “Extracorporeal photopheresis is considered investigational as a technique to treat acute graft-versus-host disease or chronic graft-versus-host disease that is either previously untreated or is responding to established therapies. Extracorporeal photopheresis is considered investigational as a technique to treat either the cutaneous or visceral manifestations of autoimmune diseases, including but not limited to scleroderma, systemic lupus erythematosus, rheumatoid arthritis, pemphigus, psoriasis, multiple sclerosis, or diabetes. Extracorporeal photopheresis is considered investigational as a technique to treat early stage (I/II) cutaneous T-cell lymphoma that is either previously untreated or is responding to established nonsystemic therapies.” Reviewed with Medical Director 8/31/2010. Notification given 9/28/2010. Policy effective date 1/4/2011. (btw)

6/21/11 Added “Solid Organ Transplant to policy name. “Description” section updated to include section regarding use in solid organ transplantation rejection. Added the following statement to the “When Covered” section; “Extracorporeal photopheresis may be considered medically necessary to treat cardiac allograft rejection, including acute

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rejection, that is either recurrent or that is refractory to standard immunosuppressive drug treatment.” Added the following information to the “When Not Covered” section; “Extracorporeal photopheresis is considered investigational in all other situations related to treatment or prevention of rejection in solid-organ transplantation.” Added “autoimmune bullous disorders” to the “Autoimmune Disease” statement as another example of when extracorporeal photopheresis is not covered. Reviewed by Medical Director 3/23/11. References added. (btw)

9/30/11 Specialty Matched Consultant Advisory Panel review 8/31/2011. No change to policy statement. (btw)

5/1/12 Policy Guidelines updated. Reference added. Medical Director review 4/12/12. (btw)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.